Low-dose aspirin use and survival in breast cancer patients: A nationwide cohort study

McMenamin, U. C., Cardwell, C. R., Hughes, C. M., & Murray, L. J. (2017). Low-dose aspirin use and survival in breast cancer patients: A nationwide cohort study. *Cancer Epidemiology*, *47*, 20-27. https://doi.org/10.1016/j.canep.2016.12.008

Published in:
Cancer Epidemiology

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

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Running title: Low-dose aspirin and breast cancer survival

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ACKNOWLEDGEMENTS:

ÚMM was supported by the Health and Social Care Research and Development, Public Health Agency, Northern Ireland. The authors would like to thank the research coordinators (Lizzie Nicholson and David Bailey) and NHS National Services Scotland for facilitating access and analysis of the Scottish cohort.

Abstract

Background: Preclinical evidence from breast cancer cell lines and animal models suggest that aspirin could have anti-cancer properties. In a large breast cancer patient cohort, we investigated whether post-diagnostic low-dose aspirin use was associated with a reduction in the risk of breast cancer-specific mortality.

Methods: We identified 15,140 newly diagnosed breast cancer patients within the Scottish Cancer Registry. Linkages to the Scottish Prescribing Information System provided data on dispensed medications and breast cancer-specific deaths were identified from National Records of Scotland Death Records. Time-dependent Cox regression models were used to calculate hazard ratios (HR) and 95% CIs for breast cancer-specific and all-cause mortality by post-diagnostic low-dose aspirin use. HRs were adjusted for a range of potential confounders including age at diagnosis, year of diagnosis, cancer stage, grade, cancer treatments received, comorbidities, socioeconomic status and use of statins. Secondary analysis investigated the association between pre-diagnostic low-dose aspirin use and breast cancer-specific and all-cause mortality.

Results: Post-diagnostic users of low-dose aspirin appeared to have increased breast cancer-specific mortality compared with non-users (HR 1.44, 95% CI 1.26, 1.65) but this association was entirely attenuated after adjustment for potential confounders (adjusted HR 0.92, 95% CI 0.75, 1.14). Findings were similar in analysis by increasing duration of use and in analysis of pre-diagnostic low-dose aspirin use.

Conclusion: In this large nationwide study of breast cancer patients, we found little evidence of an association between post-diagnostic low-dose aspirin use and cancer-specific mortality.

Keywords: low-dose aspirin; breast cancer; Scotland; pharmacoepidemiology

Abbreviations

AJCC (American Joint Committee on Cancer); BNF: British National Formulary; CI: Confidence interval; CPRD: Clinical practice research datalink; ER (oestrogen receptor), GP: General practitioner; HR: Hazard ratio; HER2 (human epidermal growth factor receptor 2), HRT: Hormone replacement therapy; ICD: International classification of diseases; NHS: National Health Service; NSS: National Services Scotland; PR (progesterone receptor)

INTRODUCTION

Evidence from preclinical models support a potential role for aspirin in the prevention of cancer progression [1]. Aspirin acts by irreversibly inhibiting both PTSG (previously COX-1) and PTSG-2, resulting in a decrease in prostaglandin production [2]. Used at low dosage, aspirin is an anti-platelet agent, widely prescribed in the primary and secondary prevention of cardiovascular disease. Platelets are important in tumour cell migration [3] and experimental data have shown that aspirin can inhibit platelet-induced adhesion of circulating tumour cells [4], and prevent metastases formation [5]. In breast cancer specifically, both *in vitro* and animal models demonstrate anti-angiogenic [6] and pro-apoptotic [7] effects for aspirin, as well as the suppression of tumour cell extravasation and tissue invasion [8].

Results from some, but not all epidemiological studies suggest that aspirin use after cancer diagnosis may possibly increase survival and/or reduce cancer recurrence in breast cancer patients. Post-diagnostic aspirin use was associated with an approximate 47% reduction in breast cancer death among postmenopausal breast cancer patients enrolled in the Iowa Women's' Health Study [9]. Within the Nurses' Health Study, a more marked 64% reduction in breast cancer mortality risk was observed in users of aspirin after diagnosis [10]. These studies were, however, based on small numbers (e.g. 26 breast cancer deaths) [9], used patient self-report of aspirin use (which may be subject to recall bias) [9, 10] and did not provide information on aspirin dose; therefore it is unclear whether the observed inverse associations are due to potential anti-platelet effects of aspirin. More recently, a study of 4,627 breast cancer patients resident in the Tayside area of Scotland reported a 58% reduction in breast cancer death associated with post-diagnostic low-dose aspirin use [11]. This particular analysis may have been partly affected by reverse causation [12], such that the true association between aspirin and cancer-specific mortality may have been exaggerated if

aspirin was withdrawn from cancer patients in whom death was suspected to be imminent [11]. In contrast to these findings, four other observational studies found little evidence of an association between aspirin use after diagnosis and breast cancer survival or recurrence [13-17]. A meta-analysis of 5 randomized controlled trials of low-dose aspirin to prevent vascular events showed that cancer patients (including patients with breast cancer) initiating aspirin treatment before cancer diagnosis had a reduced risk of metastasis and improved survival [18]. However, as these patients were taking aspirin before cancer diagnosis, it remains unclear whether low-dose aspirin use after cancer diagnosis, a time point more relevant for clinical intervention, confers any benefit.

Due to the inconsistencies and limitations of previous studies, we aimed to investigate whether post-diagnostic low-dose aspirin use was associated with a decreased risk of death from breast cancer in a large nation-wide cohort of breast cancer patients diagnosed in Scotland.

PATIENTS AND METHODS

Data sources

We conducted a retrospective cohort study which utilised linkages between national datasets from Scotland including the Scottish Cancer Registry (SMR06), the Prescribing Information System [19], the General / Acute Inpatient and Day Case dataset (SMR01), the Outpatient Attendance dataset (SMR00) and the National Records of Scotland Death Records. Information on medications was obtained from the Prescribing Information System (available from January 2009 to January 2015) which covers all medicines dispensed in the community in Scotland. Comorbidity data was retrieved from the General / Acute Inpatient and Day Case dataset (available from January 1999 to January 2015) which holds information on hospital

diagnoses and operations and the Outpatient Attendance dataset (available from January 1999 to January 2015) which contains diagnosis and procedures from new and follow up appointments at outpatient clinics. The National Records of Scotland Death Records provided mortality data and contains date and cause of death up to January 2015. The Community Health Index number (a unique number unique to individuals in Scotland) was used to link the individual data sources. The study was approved by the Privacy Advisory Committee of the National Health Service (NHS) National Services Scotland (NSS).

Study population

We identified primary breast cancer patients (ICD code C50) diagnosed between January 2009 and December 2012 within the Scottish Cancer Registry. Cohort members with previous Scottish Cancer Registry cancer diagnosis (after January 1999), apart from in situ neoplasms and non-melanoma skin cancers, were excluded. Deaths were identified from National Records of Scotland with coverage up to 1st January 2015 (or from Scottish Cancer Registry death records) with breast cancer-specific deaths defined as those with breast cancer as the underlying cause of death (ICD code C50). Deaths in the first year after breast cancer diagnosis were removed as it seemed unlikely that post-diagnostic medication usage could influence such deaths, therefore follow-up started one year after diagnosis. The patients were followed from one year after breast cancer diagnosis to death, the date they left Scotland or 1st January 2015. Patients were censored if they died from other causes (i.e. not breast cancer; ICD code C50) during follow-up.

Study design

Exposure data

Low-dose aspirin dispensed in the community (identified from the Prescribing Information System) consisted of all medications in the low-dose aspirin section of the British National Formulary (BNF) [20] (Section 2.12). A quantity of 28 tablets was assumed for the less than 0.1% of prescriptions where quantity was assumed incorrect. Post-diagnostic low-dose aspirin use was investigated as a time varying covariate [21] (patients were initially considered non-users and then users after a lag of 6 months after their first low-dose aspirin prescription). The use of a lag is recommended [22] and in this study, removed prescriptions in the 6 month period prior to death as these may reflect end of life treatment (in sensitivity analyses, the duration of this lag was varied). Therefore, all patients had a minimum of 6 months potential exposure time after diagnosis. Analyses were conducted by increasing duration of low-dose aspirin use with individuals considered non-users prior to 6 months after first use, a short term user between 6 months after first use and 6 months after the 12th prescription and a longer term user after this time.

Covariates

Data available from the Scottish Cancer Registry included AJCC cancer stage [23], histological grade and surgery, chemotherapy and radiotherapy in the six months after diagnosis. Comorbidities that contribute to the Charlson index were determined prior to diagnosis based upon ICD10 diagnosis codes, as described previously [24], in Scottish hospital inpatient (SMR01) and outpatient data (SMR00). A deprivation measure was

determined using the 2009 Scottish Index of Multiple Deprivation based upon postcode of residence [25]. Statin use was determined from dispensing records and included in all adjusted analyses due to potential associations with breast cancer-specific outcomes after diagnosis [26-28].

Statistical analysis

In the main analysis, time-dependent Cox regression models were used to calculate hazard ratios for breast cancer-specific death (HRs) and 95% confidence intervals (95% CIs) for post-diagnostic low-dose aspirin users compared with non-users using a time varying covariate as described previously. Adjusted analyses were conducted including the following potential confounders: sex, age, year of diagnosis, deprivation, grade, stage, surgery, radiotherapy, chemotherapy, aromatase inhibitor (as time varying covariate), tamoxifen (as time varying covariate), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and statin usage (as time varying covariate). Analyses were conducted by number of tablets dispensed and repeated for all-cause mortality. Subgroup analyses were conducted by cancer stage, year of diagnosis and oestrogen receptor status. Separate sensitivity analysis was conducted by additionally adjusting for tumour hormone receptor status, broadening the definition of breast cancer-specific death (i.e. if C50 was listed as any cause of death on death certificates) and increasing the lag from six months to 1 year, thereby excluding prescriptions in the year prior to death. A simplified analysis was conducted using Cox regression to compare low-dose aspirin users to non-users in the first year after breast cancer diagnosis in individuals living more than 1 year after diagnosis; this controls immortal time bias [29] without requiring time

varying covariates. An analysis was conducted based upon low-dose aspirin prescriptions in the year prior to diagnosis (excluding patients diagnosed in 2009 for whom a full year of prescription records prior to diagnosis may not be available), not excluding deaths in the first year after diagnosis. An adjusted analysis for pre-diagnostic low-dose aspirin use was first conducted omitting stage, grade, cancer treatment from adjustments for potential confounders to avoid over-adjustment [30, 31], as these could be on the causal pathway for breast cancer-specific mortality. Similar sensitivity analyses were carried out for all-cause mortality. As low-dose aspirin is primarily indicated for the primary and secondary prevention of cardiovascular disease, further analyses was conducted for only cardiovascular deaths (where the underlying cause of death was ICD 10 codes I0-99, G45, Q20-26, F01 or equivalent ICD-9 codes) and for all deaths excluding these cardiovascular deaths.

RESULTS

Patient cohort

A total of 15,140 newly diagnosed breast cancer patients met the inclusion criteria, in which there was on average 4 years of follow-up after diagnosis (sd=1, minimum=1, maximum=6 years). Patient characteristics by post-diagnostic low-dose aspirin use are shown in Table 1. Low-dose aspirin users were more likely to be older and to be from deprived areas. Compared to non-users, a slightly smaller proportion of low-dose aspirin users were diagnosed with early stage tumours (34.6% versus 40.1%, respectively) while a slightly larger proportion of users were diagnosed with poorly differentiated tumours (29.3% versus 35.7%, respectively). Low-dose aspirin users were less likely to receive cancer treatments (including surgery, chemotherapy and tamoxifen); however they were more likely to receive aromatase inhibitors. A greater proportion of low-dose aspirin users compared to non-users

had comorbidities (particularly for cerebrovascular disease, diabetes and myocardial infarction) and were users of statins.

Association between low-dose aspirin use after diagnosis and survival

The main findings are displayed in Table 2. Low-dose aspirin use after diagnosis was associated with an increase in breast cancer-specific mortality (HR 1.44, 95% CI 1.26, 1.65); however after adjusting for age at diagnosis results attenuated to the null (age adjusted HR 1.03, 0.88, 1.18). After adjustment for potential confounders the HR was 0.92 (95% CI 0.75, 1.14), Table 2. No significant duration-response association was observed when exposure was investigated by increasing number of tablets. There was a suggestion of a significant reduction in breast cancer mortality risk with the use of 730-1,095 aspirin tablets (adjusted HR 0.55, 95% CI 0.32, 0.96); however, the increasing duration of use analysis did not follow a clear pattern and the reduction in breast cancer mortality risk was not observed for users of 1,095+ tablets (adjusted HR 1.22, 95% CI 0.75, 2.00).

Similarly, post-diagnostic low-dose aspirin use was associated with an increase in all-cause mortality (HR 2.18, 95% CI 1.99, 2.40) which weakened in adjusted analysis but remained statistically significant (adjusted HR 1.21 1.04, 1.40). In duration-response analysis, a 26% increased risk of death was seen for users of 1-365 tablets after diagnosis, however results attenuated and became non-significant among users of , 365-730 tablets and 730-1,095 tablets, Table 2. For users of 1,095 tablets (i.e. more than 3 years of use), a significant increase in breast cancer mortality was observed (adjusted HR 1.44, 95% CI 1.03, 2.03). . Further analyses (shown in Table 4) suggested that the increase in all-cause mortality observed for low-dose aspirin users was largely due to cardiovascular deaths (adjusted HR

1.73, 95 % CI 1.19, 2.50) and once these deaths were removed, there was no increase in all-cause mortality in users compared to non-users (adjusted HR 1.11; 95 % CI 0.94–1.31).

Association between low-dose aspirin use before diagnosis and survival

Results for low-dose aspirin use in the year preceding diagnosis are shown in Table 3. In adjusted models, there was little evidence of an association between low-dose aspirin use before diagnosis and cancer-specific mortality (adjusted HR 0.95, 85% CI 0.81, 1.11). For all-cause mortality, a significant increase in risk was observed for low-dose aspirin users before diagnosis (HR 2.33, 95% CI 2.12, 2.56).

Sensitivity\secondary analyses for low-dose aspirin use after diagnosis and survival

Table 4 summarises results for sensitivity\secondary analyses. In comparison to the main analysis, stratification by cancer stage, year of diagnosis and hormone receptor status did not materially alter associations between post-diagnostic low-dose aspirin use after diagnosis and cancer-specific mortality. Similar effect estimates were observed after additional adjustment for ER, PR and HER2 status, after broadening the definition of breast cancer-specific death, as well as in analysis increasing the lag to 1 year. In the simple analysis, low-dose aspirin use compared to non-use in the year after diagnosis was not associated with cancer-specific mortality, Table 4. For all-cause mortality, similar to the main analysis, an increase in breast cancer mortality risk was observed for post-diagnostic low-dose aspirin use across sub-group and sensitivity analyses, however; as described earlier, this is likely driven by cardiovascular deaths, Table 4.

DISCUSSION

Our study, which utilised prospectively recorded information from national cancer, death and drug dispensing registries, found little evidence of an association between the use of low-dose aspirin after diagnosis and breast cancer-specific mortality. We did not observe any clear relationship by increasing duration of use and results were similar across a number of sub-group and sensitivity analyses.

Our results are contrary to some, but not all previous epidemiological studies of post-diagnostic aspirin use and breast cancer-specific survival. Data from two American cohorts, the Nurses' Health Study [10] and the Iowa Women's Health Study [9] reported substantial reductions in breast cancer mortality in users of aspirin after diagnosis compared to non-users. These studies restricted their cohorts to patients diagnosed with early stage breast cancer and obtained information on aspirin exposure through questionnaires. Hence, differences in patient populations and study methodologies make comparisons with our findings difficult. Moreover, there was a lack of information on aspirin dose used in these studies although high-dose aspirin is more commonly used in the USA in comparison to the UK [32]. It is possible that the extended breast cancer survival observed for aspirin users in these studies may be due to higher PTSG-2 inhibiting doses as opposed to doses which inhibit platelet function. Our study also contradicts the results from a recent Scottish study which observed an approximate 60% reduction in cancer mortality among users of low-dose aspirin use after diagnosis (adjusted HR 0.42, 95% CI 0.31, 0.55) [11]. Like ours, this study utilised linked cancer registration and dispensed medication data, but their findings may have partly been affected by reverse causation as they utilised an unlagged start/stop time-varying covariate approach which allocated cancer-specific deaths to the aspirin user or nonuser group on the basis of whether they had an aspirin prescription that covered the time of death.

As such, if clinicians discontinued aspirin medication in patients suspected of imminent death, the use of unlagged time-varying covariates could potentially bias results making aspirin appear spuriously protective [12]. In our analysis, we lagged medication use after diagnosis by 6 months and this period was varied in sensitivity analysis. Other epidemiological studies have reported no association for aspirin use after diagnosis and risk of breast cancer death [15, 16, 17]. Similar to our investigation, these studies assessed the impact of low-dose aspirin specifically and drug use was captured using population-based prescribing databases. We found that low-dose aspirin use after diagnosis was associated with a slight increase in all-cause mortality risk but the findings may reflect risk of death from other (non-cancer) causes, as suggested by the observed increase in cardiovascular deaths in users of low-dose aspirin.

In secondary analysis, we did not observe an association between aspirin use in the year prior to diagnosis and breast cancer-specific mortality, which is in agreement with a previous large population-based study we conducted within the Clinical Practice Research Datalink (CPRD) [15]. In contrast, in a cohort of stage I-III patients diagnosed in Ireland, aspirin use (predominantly low-dose) in the year prior to diagnosis was associated with a weak non-significant reduction in breast cancer mortality (HR 0.80, 95% CI 0.62, 1.04) [33]. In a further study of 935 breast cancer patients enrolled in the Carolina Breast Cancer Study, increased duration and regularity of self-reported pre-diagnostic NSAID use (including aspirin) was associated with reduced breast cancer-specific mortality in women with ER-positive tumours while no association was seen for women with ER-negative tumours [34]. The authors of this study however did not examine the influence of aspirin separately. The potential anti-cancer effect of aspirin has been hypothesised to be, in part, mediated through

suppression of oestrogen biosynthesis [35, 36], but similar to our study, two previous cohort studies found no difference in associations by hormone receptor status [10, 17].

Strengths of this study included the utilisation of an unselected population-wide cohort of breast cancer patients identified from national cancer registries, therefore allowing for robust verification of breast cancer cases. Prospective national prescribing databases were used to objectively ascertain aspirin use and avoid potential for recall bias incurred by self-report. It also facilitated detailed examination of the timing of aspirin use, as well as the conduct of duration-response analyses. Misclassification of drug use is possible as over-the-counter use of low-dose aspirin was not accounted for, although previous evidence suggests that the majority of chronic aspirin use in administrative prescribing databases is captured [37]. In Scotland specifically, long-term aspirin use has been shown to be primarily prescription-based [38]. Some misclassification of breast cancer deaths may have occurred, however methodological studies have suggested that in comparative studies where differential misclassification of death is unlikely, as in our study, effect estimates are unlikely to be affected [39]. Confounding by indication, often a problem in pharmacoepidemiology, is unlikely to have influenced our main finding for breast cancer-specific mortality, but would explain the small increases in all-cause mortality primarily due to raised cardiovascular mortality in low-dose aspirin users. Finally, we did not have information on drug adherence but similar associations were observed among patients who received multiple prescriptions in whom adherence may be more likely.

Conclusion

In this large nation-wide cohort of breast cancer patients, we found little evidence of a reduction in cancer-specific mortality with the use of low-dose aspirin after diagnosis. The recently opened ‘Add Aspirin’ trial will investigate the influence of low dose aspirin (100mg and 300mg) in early stage cancer patients (including breast) and will provide additional insight into the potential role of aspirin in the adjunct cancer setting [40]. Further, large-scale, rigorously designed observational studies of aspirin in breast cancer progression are warranted however, as the results from this trial are not due until 2020.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTION

- Conception and design of the study: CR Cardwell, LJ Murray, CM Hughes
- Acquisition of data: CR Cardwell, LJ Murray, CM Hughes
- Analysis and/or interpretation of data: CR Cardwell, ÚC Mc Menamin
- Manuscript preparation: ÚC Mc Menamin
- Revision of the manuscript: ÚC Mc Menamin, CR Cardwell, LJ Murray, CM Hughes
- Final approval of the version to be published: ÚC Mc Menamin, CR Cardwell, LJ Murray, CM Hughes

References

1. L.J. Gay, B. Felding-Habermann, Platelets alter tumor cell attributes to propel metastasis: programming in transit, Cancer Cell. 20 (2011) 20:553-4, doi: 10.1016/j.ccr.2011.11.001.

2. D.L. Simmons, R.M. Botting, T. Hla, Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition, Pharmacol Rev. 56 (2004) 387-437, doi: 10.1124/pr.56.3.3.

3. N.M. Bambace, C.E. Holmes, The platelet contribution to cancer progression, J Thromb Haemost. 9 (2011) 237-49, doi: 10.1111/j.1538-7836.2010.04131.x.

4. F.P. Lloyd Jr, V. Slivova, T. Valachovicova, D. Sliva, Aspirin inhibits highly invasive prostate cancer cells, Int J Oncol. 23 (2003) 1277-83, doi: 10.3892/ijo.23.5.1277.

5. S. Mezouar, R. Darbousset, F. Dignat-George, L. Panicot-Dubois, C. Dubois, Inhibition of platelet activation prevents the P-selectin and integrin-dependent accumulation of cancer cell microparticles and reduces tumor growth and metastasis in vivo, Int J Cancer. 136 (2015) 462-75, doi: 10.1002/ijc.28997.

6. F. Ghezzo, L. Cesano, B. Mognetti, E. Pesce, E. Pirro, G. Corvetti, G.N. Berta, B. Zingaro, F. Di Carlo, Salicylate inhibition of rat mammary carcinogenesis and angiogenesis in female rat compatible with misoprostol administration, Int J Oncol. 26 (2005) 697-702, doi: 10.3892/ijo.26.3.697.

7. M. Chattopadhyay, R. Kodela, N. Nath, A. Barsegian, D. Boring, K. Kashfi, Hydrogen sulfide-releasing aspirin suppresses NF-κB signaling in estrogen receptor negative

breast cancer cells in vitro and in vivo, Biochem Pharmacol. 83 (2012) 723-732, doi: 10.1016/j.bcp.2011.

8. I. Lal, K. Dittus, C.E. Holmes, Platelets, coagulation and fibrinolysis in breast cancer progression, Breast Cancer Res. 15 (2013) 207, doi:10.1186/bcr3425.

9. C.K. Blair, C. Sweeney, K.E. Anderson, A.R. Folsom, NSAID use and survival after breast cancer diagnosis in post-menopausal women, Breast Cancer Res Treat. 101 (2007) 191-197, doi: 10.1007/s10549-006-9277-x.

10. M.D. Holmes, W.Y. Chen, L. Li, E. Hertzmark, D. Spiegelman, S.E. Hankinson, Aspirin Intake and Survival After Breast Cancer, J Clin Oncol. 28 (2010) 1467-1472, doi: 10.1200/JCO.2009.22.7918.

11. D.M. Fraser, F.M. Sullivan, A.M. Thompson, C. McCowan, Aspirin use and survival after the diagnosis of breast cancer: a population-based cohort study, Br J Cancer. 111(2014) 623-627, doi: 10.1038/bjc.2014.264.

12. H. Tamim, A.A., Monfared, J. LeLorier, Application of lag-time into exposure definitions to control for protopathic bias, Pharmacoepidemiol Drug Saf. 16 (2007) 250-8, doi: 10.1002/pds.1360.

13. M.L. Kwan, L.A. Habel, M.L. Slattery, B. Caan, NSAIDs and breast cancer recurrence in a prospective cohort study, Cancer Causes Control. 18 (2012) 613-620, doi:10.1007/s10552-007-9003-y.

14. K.J. Wernli, J.M. Hampton, A. Trentham-Dietz, P.A. Newcomb, Use of antidepressants and NSAIDs in relation to mortality in long-term breast cancer survivors, Pharmacoepidemiol Drug Saf. 20 (2011)131-7, doi: 10.1002/pds.2064.

15. L.J. Murray, J.A. Cooper, C.M. Hughes, D.G. Powe, C.R. Cardwell, Post-diagnostic prescriptions for low-dose aspirin and breast cancer-specific survival: a nested case-control study in a breast cancer cohort from the UK Clinical Practice, Breast Cancer Res 16 (2014) R34, doi:10.1186/bcr3638.

16. M.D. Holmes, H. Olsson, Y. Pawitan, J. Holm, C. Lundholm, T.M. Andersson, H.O. Adami, J. Askling, K.E. Smedby, Aspirin intake and breast cancer survival – a nation-wide study using prospectively recorded data in Sweden, BMC Cancer. 14 (2014) 391, doi:10.1186/1471-2407-14-391.

17. T.I. Barron, L.M Murphy, C. Brown, K. Bennett, K. Visvanathan, L. Sharp, De Novo Post-Diagnosis Aspirin Use and Mortality in Women with Stage I-III Breast Cancer, Cancer Epidemiol Biomarkers Prev. 24 (2015) 898-904, doi: 10.1158/1055-9965.EPI-14-1415.

18. P.M. Rothwell, M. Wilson, J.F. Price, J.F.F. Belch, T.W. Meade, Z. Mehta, Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials, Lancet. 379 (2012) 1591-601, doi: 10.1016/S0140-6736(12)60209-8.

19. S. Alvarez-Madrazo, S. Mc Taggart, C. Nangle, E. Nicholson, M. Bennie, Data Resource Profile: The Scottish National Prescribing Information System (PIS), Int J Epidemiol. 45 (2016) 714-715f, doi: 10.1093/ije/dyw060.

20. Joint Formulary Committee, British National Formulary (2014) BMJ Publishing Group Ltd.

21. L.E. Levesque, J.A. Hanley, A. Kezouh, S. Suissa, Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes, BMJ. 340 (2010) b5087, doi: 10.1136/bmj.b5087.

22. J. Chubak, D.M. Boudreau, H.S. Wirtz, B. McKnight, N.S. Weiss, Threats to Validity of Nonrandomized Studies of Postdiagnosis Exposures on Cancer Recurrence and Survival, J Natl Cancer Inst. 105 (2013) 1456-1462. doi: 10.1093/jnci/djt211.

23. S. B. Edge, C.C. Compton, The AJCC Cancer Staging Manual and Handbook: 7th Edition (2010) New York: Wiley-Liss.

24. V. Sundararajan, T. Henderson, C. Perry, A. Muggivan, H. Quan, W.A. Ghali, New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality, J Clin Epidemiol. 57 (2004) 1288-1294, doi: 10.1016/j.jclinepi.2014.09.017.

25. R.R. Donnelly, Scottish Index of Multiple Deprivation 2009: General Report. Edinburgh (2009) UK: A Scottish Government National Statistics Publication.

26. T.P. Ahern, L. Pedersen, M. Tarp, et al., Statin prescriptions and breast cancer recurrence risk: A Danish nationwide prospective cohort study, J Natl Cancer Inst. 103 (2011) 1461-1468, doi: 10.1093/jnci/djr291.

27. T.J. Murtola, K. Visvanathan, M. Artama, H. Vainio, E. Pukkala, Statin use and breast cancer survival: a nationwide cohort study from Finland, PLoS One. 9 (2014) e110231, doi: 10.1371/journal.pone.0110231.

28. C.R. Cardwell, B.M. Hicks, C. Hughes C, L.J. Murray, Statin use after diagnosis of breast cancer and survival: a population-based cohort study, Epidemiology. 26 (2015) 68-78, doi: 10.1097/EDE.0000000000000189.

29. Z. Zhou, E. Rahme, M. Abrahamowicz, L. Pilote, Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods, Am J Epidemiol. 162 (2005) 1016-1023, doi: 10.1093/aje/kwi307.

30. C.R.Weinberg, Toward a clearer definition of confounding, Am J Epidemiol. 137 (1993) 137:1-8, doi:10.1093/aje/kws127.

31. E.F. Schisterman, S.R. Cole, R.W. Platt, Overadjustment bias and unnecessary adjustment in epidemiologic studies, Epidemiology. 20 (2009) 488-495, doi: 10.1097/EDE.0b013e3181a819a1.

32. R. Paulose-Ram, R. Hirsch, C. Dillon, Q. Gu, Frequent monthly use of selected non-prescription and prescription non-narcotic analgesics among U.S. adults, Pharmacoepidemiol Drug Saf. 14 (2005) 257-66, doi: 10.1002/pds.983.

33. T.I. Barron, E.M. Flahavan, L. Sharp, K. Visvanathan, Recent prediagnostic aspirin use, lymph node involvement, and 5-year mortality in women with stage I-III breast cancer: a nationwide population-based cohort study, Breast Cancer Res Treat. 74 (2014) 4065-77, doi: 10.1158/0008-5472.

34. E.H. Allott, C.K. Tse, A.F. Olshan, L.A. Carey, P.G. Moorman, M.A.Trouster, Non-steroidal anti-inflammatory drug use, hormone receptor status, and breast cancer-specific mortality in the Carolina Breast Cancer Study, Breast Cancer Res Treat. 147 (2014) 415-421, doi: 10.1007/s10549-014-3099-z.

35. A.G. Hudson, G.L. Gierach, F. Modugno, J. Simpson, J.W. Wilson, R.W. Evans, V.G. Vogel, J.L. Weissfeld, Nonsteroidal Anti-inflammatory Drug Use and Serum Total Estradiol in Postmenopausal Women, Cancer Epidemiol Biomarkers Prev. 17 (2008) 680-687, doi: 10.1158/1055-9965.

36. G. Davies. Cyclooxygenase-2 (COX-2), aromatase and breast cancer: a possible role for COX-2 inhibitors in breast cancer chemoprevention, Ann Oncol. 13 (2002) 669-678, doi: 10.1093/annonc/mdf125.

37. Y. Yang, S.H. Pharmd, K. Propert, W. Hwang, M. Sarkar, J.D. Lewis, Chronic statin therapy and the risk of colorectal cancer, Pharmacoepidemiol Drug Saf. 17 (2008) 869–76, doi: 10.1002/pds.1599.

38. S.V. Morant, A.D. McMahon, J.G.F. Cleland, P.G. Davey PG, T.M. MacDonald, Cardiovascular prophylaxis with aspirin: costs of supply and management of upper gastrointestinal and renal toxicity, Br J Clin Pharmacol. 57 (2003) 188-198, doi: 10.1046/j.1365-2125.2003.01979.x.

39. D. Sarfati, T. Blakely, N. Pearce, Measuring cancer survival in populations: relative survival vs cancer-specific survival, Int J Epidemiol. 39 (2010) :598–610, doi: 10.1093/ije/dyp392.

40. R.E. Langley, R.H. Wilson, A. Ring, H.G. Kynaston, C.M. Murphy, D.A. Cameron, F.H. Cafferty, M.K. Parmar, Evidence for the use of aspirin as a treatment for cancer and the planned Add-Aspirin trial, First World Congress on Controversies in Gastroenterology (2013) Berlin, Germany, Available at: http://www.comtecmed.com/cigi/2013/Abstracts_Text.aspx. Accessed October 5, 2015.

Table 1. Characteristics of breast cancer patients by post-diagnostic low-dose aspirin use

	Low-dose aspirin use in the year after diagnosis[a]			
	User		Non-user	
	n	%	n	%
Year of diagnosis				
2009	638	27.1	3,034	23.7
2010	605	25.7	3,121	24.4
2011	566	24.0	3,283	25.7
2012	545	23.2	3,348	26.2
Age at diagnosis				
<50	43	1.9	2,791	21.8
50-59	209	8.9	3,484	27.2
60-69	668	28.4	3,604	28.2
70-79	752	31.9	1,838	14.4
80-89	561	23.8	894	7.0
≥ 90	121	5.1	175	1.4
AJCC stage				
1	815	34.6	5126	40.1
2	824	35	4887	38.2
3	271	11.5	1491	11.7
4	93	4	491	3.8
Missing	351	14.9	791	6.2
Grade				
1	290	12.3	1539	12
2	1047	44.5	5739	44.9
3	690	29.3	4565	35.7
Missing	327	13.9	943	7.4
Deprivation				
1 (most deprived)	537	22.8	1,975	15.4
2	528	22.4	2,386	18.7
3	462	19.6	2,652	20.7
4	456	19.4	2,829	22.1
5 (least deprived)	371	15.8	2,943	23.0
Treatment (within 6 months)				
Surgery	1,665	70.7	10,734	84.0
Radiotherapy	911	38.7	4,659	36.4
Chemotherapy	351	14.9	5,076	39.7
Comorbidity prior to diagnosis				
Acute myocardial infarction	234	9.9	71	0.6
Congestive heart failure	122	5.2	103	0.8
Peripheral vascular disease	89	3.8	75	0.6
Cerebral vascular accident	216	9.2	187	1.5
Pulmonary disease	222	9.4	582	4.6
Petptic ulcer	52	2.2	153	1.2
Liver disease	8	0.3	17	0.1
Diabetes	289	12.3	262	2.0
Renal disease	86	3.7	99	0.8
Medication use in year after diagnosis				
Statins[b]	1,617	68.7	2,007	15.7
Aromatase inhibitors	1,524	64.7	5,284	41.3
Tamoxifen	645	27.4	5,697	44.6

[a] Post-diagnostic low-dose aspirin use in the year after diagnosis among breast cancer patients who lived more than 1 year after diagnosis. [b] Statin use in year after diagnosis for low-dose aspirin use in year after diagnosis columns, statin use in year prior to diagnosis for low-dose aspirin use in year prior to diagnosis columns.

Table 2. Association between low-dose aspirin use after diagnosis and cancer-specific and all-cause mortality in patients with breast cancer.

	Mortality	Patients	Person years	Unadjusted HR (95% CI) *[n=15,140]*	P	Adjusted[a] HR (95%CI) *[n=13,039]*	P
Cancer-specific mortality							
Low-dose aspirin non-user	929	12,318	34,452	1.00 (ref. cat.)		1.00 (ref. cat.)	
Low-dose aspirin user	261	2,822	6,821	1.44 (1.26, 1.65)	<0.001	0.92 (0.75,1.14)	0.468
1-365 tablets	120	836	2,853	1.50 (1.24, 1.82)	<0.001	0.98 (0.74,1.30)	0.889
365-730 tablets	91	692	2,098	1.55 (1.24, 1.93)	<0.001	0.93 (0.68, 1.29)	0.68
730-1,095 tablets	25	548	1,074	0.93 (0.62, 1.39)	0.73	0.55 (0.32,0.96)	0.04
1,095+ tablets	25	746	796	1.57 (1.04, 2.38)	0.03	1.22 (0.75, 2.00)	0.43
All-cause mortality							
Low-dose aspirin non-user	1405	12,318	34,452	1.00 (ref. cat.)		1.00 (ref. cat.)	
Low-dose aspirin user	602	2,822	6,821	2.18 (1.99, 2.40)	<0.001	1.21 (1.04,1.40)	0.015
1-365 tablets	252	836	2,852	2.11 (1.84, 2.42)	<0.001	1.26 (1.03,1.54)	0.022
365-730 tablets	194	692	2,098	2.22 (1.90, 2.58)	<0.001	1.14 (0.91, 1.43)	0.26
730- 1,095 tablets	90	548	1,074	2.17 (1.74, 2.70)	<0.001	1.04 (0.76, 1.43)	0.79
1,095+ tablets	66	746	796	2.44 (1.88, 3.16)	<0.001	1.44 (1.03, 2.03)	0.03

[a]Model contains age, year of diagnosis, deprivation, stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease), hormone replacement therapy use (in year prior to diagnosis) and other prescription medication use (tamoxifen, aromatase inhibitor and statin use, as time varying covariates).

Table 3. Association between low-dose aspirin use before diagnosis and cancer-specific and all-cause mortality in patients with breast cancer.

	Mortality	Patients	Person years	Unadjusted HR (95% CI)	P	Adjusted[a] HR (95%CI)	P
				[n=12,231]		*[n=12,231]*	
Cancer-specific mortality							
Low-dose aspirin non-user	940	10,264	32,771	1.00 (ref. cat.)		1.00 (ref. cat.)	
Low-dose aspirin user	275	1,967	5,652	1.68 (1.47, 1.92)	<0.001	0.95 (0.81,1.11)	0.51
All-cause mortality							
Low-dose aspirin non-user	1,445	10,264	32,771	1.00 (ref. cat.)		1.00 (ref. cat.)	
Low-dose aspirin user	586	1,967	5,652	2.33 (2.12, 2.56)	<0.001	1.10 (0.98,1.23)	0.107

[a]Model contains age, year of diagnosis, deprivation, comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disaese, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and statin use and hormone replacement therapy use (in year prior to diagnosis).

Table 4. Sensitivity analysis of association between low-dose aspirin use after diagnosis and cancer-specific and all-cause mortality in patients with breast cancer.

	Medication user			Medication non-user			Unadjusted HR 95% CI)	P	Adjusted[a] HR (95%CI)	P	P interaction
	Cancer \ all mortality	Patients	Person years	Cancer \ all mortality	Patients	Person years					
Cancer-specific mortality											
Subgroup analyses: Aspirin users versus non-users											
Stage 1	15	988	2,566	88	4,953	14,358	0.94 (0.55,1.63)	0.836	0.74 (0.35,1.54)	0.415	
Stage 2	67	999	2,484	251	4,712	13,445	1.45 (1.11,1.90)	0.007	1.13 (0.79,1.62)	0.506	0.22
Stage 3	62	329	747	281	1,433	3,771	1.13 (0.86,1.49)	0.383	0.85 (0.60,1.22)	0.383	
Stage 4	43	111	208	186	473	933	1.10 (0.79,1.53)	0.578	0.77 (0.44,1.35)	0.363	
Diagnosed 2009-2010	186	1,569	4,670	590	5,829	21,897	1.50 (1.27, 1.77)	<0.001	1.05 (0.81,1.36)	0.725	0.56
Diagnosed 2011-2012	75	1,253	2,151	339	6,489	12,555	1.30 (1.01, 1.67)	0.04	0.72 (0.48,1.06)	0.095	
Oestrogen receptor positive	185	2,423	5,887	610	10,227	28,793	1.49 (1.27, 1.76)	<0.001	0.91 (0.70,1.19)	0.505	
Hormone receptors available[b] (and adjusted for)	158	1,668	3,860	604	7,860	21,015	1.44 (1.21, 1.72)	0.99	0.91 (0.69,1.20)	0.51	
Using 1 year lag[c]	240	2691	6300	950	12449	34973	1.44 (1.25,1.66)	<0.001	0.90 (0.72,1.12)	0.361	
Breast cancer listed as any cause of death	392	2,822	6,821	1,159	12,318	34,452	1.73 (1.54,1.94)	<0.001	1.06 (0.89,1.28)	0.499	
Use in first year after diagnosis[d]											
Aspirin user versus non-user	237	2354	6128	953	2354	35146	1.42 (1.23,1.64)	<0.001	0.90 (0.72,1.12)	0.329	
All-cause mortality											
Subgroup analyses: Aspirin users versus non-users[a]											
Stage 1	72	988	2566	217	4953	14358	1.84 (1.41,2.40)	<0.001	0.91 (0.65,1.28)	0.588	
Stage 2	170	999	2484	392	4712	13445	2.35 (1.96,2.81)	<0.001	1.46 (1.15,1.85)	0.002	0.02
Stage 3	110	329	747	335	1433	3771	1.67 (1.35,2.08)	<0.001	1.18 (0.88,1.57)	0.273	
Stage 4	57	111	208	207	473	933	1.31 (0.97,1.75)	0.074	0.92 (0.55,1.51)	0.733	
Diagnosed 2009-2010	429	1,569	4,670	898	5,829	21,897	2.26 (2.01, 2.53)	<0.001	1.21 (1.01,1.46)	0.038	0.61
Diagnosed 2011-2012	173	1,253	2,151	507	6,489	12,555	2.00 (1.68, 2.38)	<0.001	1.16 (0.88,1.52)	0.299	
Oestrogen receptor positive	477	2,423	5,887	1,018	10,227	28,793	2.30 (2.06, 2.56)	<0.001	1.22 (1.02,1.45)	0.026	
Hormone receptors available[b] (and adjusted for)	335	1,668	3,860	871	7,860	21,014	2.11 (1.86, 2.39)	<0.001	1.21 (0.99,1.47)	0.057	
Cardiovascular deaths	134	2822	6821	140	12318	34452	4.88 (3.85,6.18)	<0.001	1.73 (1.19,2.50)	0.004	
Non- cardiovascular deaths	468	2822	6821	1265	12318	34452	1.89 (1.70,2.10)	<0.001	1.11 (0.94,1.31)	0.221	
Using 1 year lag[c]	554	2691	6300	1453	12449	34973	2.16 (1.96,2.38)	<0.001	1.17 (1.00,1.37)	0.045	
Use in first year after diagnosis[d]											
Aspirin user versus non-user	550	2354	6128	1457	2354	35146	2.16 (1.96,2.38)	<0.001	1.17 (1.00,1.37)	0.047	

[a]Based upon main time varying covariate analysis adjusted model contains age, year of diagnosis, deprivation, stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) hormone replacement therapy use (in year prior to diagnosis) and other prescription medication use (tamoxifen, aromatase inhibitor and statins, as time varying covariates).
[b]Model contains all variables in [1] along with oestrogen, progesterone and HER2 receptor status, where available.
[c]Low-dose aspirin use modelled as a time varying covariate with a 1 year lag. Model contains all variables in [1] with prescription medication use all modelled with a 1 year lag (tamoxifen, aromatase inhibitor, and statin use).
[d]Model contains age, year of diagnosis, deprivation, stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) hormone replacement therapy use (in year prior to diagnosis) and other prescription medication use in the first year after diagnosis (tamoxifen, aromatase inhibitor and statin use).